SUMMARY MINUTES

OF THE

MEDICAL DEVICES DISPUTE RESOLUTION PANEL

OPEN SESSION

September 6, 2001

Salons E, F and G

Gaithersburg Marriott

9751 Washingtonian Blvd.

Gaithersburg, Maryland

Medical Devices Dispute Resolution Panel
September 6, 2001

Panel Participants

Scott D. Ramsey, MD, PhD
Acting Panel Chair

Mark D. Carlson, MD, MA
Voting Member

Ralph B. D'Agostino, PhD
Temporary Voting Member

Gerald J. Shirk, MD
Temporary Voting Member

Kim L. Thornton, MD
Temporary Voting Member

Hector Hugo Gonzalez, RN, PhD
Consumer Representative

Judy Gordon, DVM
Industry Representative

FDA Participants

Les Weinstein, Esq
CDRH Ombudsman and
Executive Secretary, Medical Devices Dispute Resolution Panel

David Kraus, PhD
Office of Device Evaluation

Roxolana Horbowyj, MD
Office of Device Evaluation

Richard Kotz
Office of Surveillance and Biometrics

OPEN SESSION

Acting Panel Chair Scott Ramsey, MD, PhD, called the session to order at 8:08 AM by reading the summary of the scientific issues in dispute. He noted on November 15, 2000 the Office of Device Evaluation (ODE) in FDA's Center for Devices and Radiologic Health sent Lifecore Biomedical a "not approvable" letter for its Premarket Approval Application (PMA) P990015, Intergel Adhesion Prevention Solution.

In the process of determining the safety and effectiveness of this device, today's panel would have to determine 1) whether there is a clinically significant difference between Intergel Solution and the control and 2) whether the benefits outweigh the potential risks (in particular, the risk of infection) of this device.

Dr. Ramsey asked the panel members to introduce themselves, which they did.

Panel Executive Secretary Les Weinstein read for the record temporary voting status for Drs. D'Agostino, Shirk and Thornton. He then read the conflict of interest statement and noted that a waiver was granted to Dr. D'Agostino. The agency had taken into consideration other matters regarding Drs. Carlson and D'Agostino and had allowed their full participation in today's panel meeting.

OPEN PUBLIC HEARING

Michael Kettel, MD, a Principal Investigator of Intergel stated that this product reduced adhesions at the surgical site and also at distant sites from the surgical area.

Lena Holmdahl, MD, PhD, a medical researcher of adhesion formation and treatment of adhesions in Goteborg, Sweden noted that due to various reasons, clinical outcome studies cannot be completed in the pre-market approval phase of this device.

Russell Malinak, MD, an emeritus professor of Obstetrics and Gynecology at Baylor College of Medicine, had participated in the Intergel Pivotal Study and found the product both safe and effective. He added that the study was well designed, chose the right outcome (the adhesions), and focused on the appropriate site (the adnexa).

Dr. Melvin Thornton, Assistant Professor of Women's Reproductive Care at Columbia University, was an Intergel Study participant who, not only thought that the device was safe and effective, but also easy to use.

Panel Executive Secretary Les Weinstein read letters supporting the approval of Intergel from the American Society of Reproductive Medicine and from the Pacific Gynecology Specialist Group in Seattle, Washington.

Sponsor Presentations

PREMARKET APPROVAL APPLICATION P990015/A10 [11] LIFECORE BIOMEDICAL, INC.'s INTERGEL Adhesion Prevention Solution

Dr. Karen Becker summarized the sponsor's position on scientific issues by detailing the significance of intraperitoneal adhesions and presenting the sequence of the approval process of this device. Since the General and Plastic Surgery Devices Panel meeting of January 12, 2000, an animal study was completed that demonstrated no increased incidence of infection, and the intended use of Intergel has changed from general surgery to gynecologic pelvic surgery.

Dr. Douglas Johns reviewed the results of the Pivotal Clinical Trial. In this blinded, multi-center study the safety of this device was comparable to the control (lactated Ringer's solution). Efficacy was established since both the number of adhesions and the treatment failures were reduced.

Beginning the clinical presentation, **Dr. Luigi Mastroianni** stated that eight medical experts independently reviewed the data of this trial. Their consensus opinion stated that, in addition to Intergel being safe and effective, the study design, execution, and analysis yielded valid data.

Dr. Alan DeCherney reported the methodology used in this trial was valid and conformed with that of the American Fertility Society. He asserted that the risk of moderate to severe adnexal adhesions decreased five-fold with the use of Intergel compared with the control solution.

Dr. Sebastian Faro addressed the safety issue by concluding that Intergel was as safe as the control. The animal study revealed no post-operative infections.

Dr. Ted Colton introduced the six statistical issues studied by a group of experts retained by Lifecore. The consensus opinion of this statistical group concluded that the clinical trial was well designed and the analyses were scientifically sound.

Dr. Steven Piantadosi thought the Pivotal Study featured a well-designed trial with good adherence to the protocol. The data from Europe and the US can be pooled because both locations employed a common protocol and produced a common treatment effect.

Dr. Ted Colton stated the power calculations for the Pilot Study and the Pivotal Study were valid and correct as calculated.

Dr. Donald Rubin noted that the FDA treated the Intention-to-Treat (ITT) patients or the 6% who did not have a second look procedure as worst-case outcomes. While this technique unfavorably skews the outcome of the trial, Dr. Rubin's blinded analysis results in a favorable outcome which is similar to that of the patients who had second-look procedures.

The panel members questioned the sponsor about the stability of the analysis, the low drop out rate in the Pivotal Trial, and how the protocol would by rewritten retrospectively.

FDA Presentations

After mentioning the original indications for the device and the new indications in the present PMA submission, **Dr. David Kraus** introduced the FDA presenters.

Dr. Roxolana Horbowyj reviewed the pathophysiology of adhesions and the American Fertility Society (AFS) scoring system, together with the modified and retrospective scoring systems employed in the Intergel study. Reviewing both the Pilot and Pivotal Studies, she noted in the Pivotal Study, the European and American cohorts are not comparable with respect to race, incidence of baseline number of adhesions, or type of surgical procedure. Since the occurrence of moderate to severe post-operative adhesions is rare in this patient population, comparing the resulting small numbers may be clinically insignificant. In some instances, the difference in outcome between Intergel and the control was even less than one adhesion.

Richard Kotz restated the original study protocol and reviewed 1) the primary endpoint, modified AFS (mAFS) scores, 2) secondary endpoint, number of adhesions,

and 3) additional endpoints, subsets of adhesions (reformed, de novo, and surgical site adhesions.) The sponsor's proposed protocol and analysis plan was to include 200 US subjects and 80 European subjects and was to assign worst scores to subjects lost to follow-up, Intent-to treat (ITT) group. The sponsor stipulated three conditions: 1) baseline demographic pretreatment variables (including adhesion scores) should be similar between the device and control, 2) no significant interactions should occur between the continents with respect to treatment efficacy, and 3) the second look scores should be similar between the device and control.

Because the baseline values are statistically different and an interaction does occur between the change from the baselines, the data should not be pooled between the continents. The analysis of the data from US ITT outcome of mAFS scores and number of adhesions reveals no significant difference between Intergel and control. From this analysis, the secondary endpoint data also becomes questionable. The number of patients with moderate to severe adhesions forms too small a group to be statistically meaningful.

The panel questioned the FDA presenters about the appropriateness of pooling the data between continents and the FDA's concentration on the ITT group when three cohorts were outlined in the protocol.

Sponsor Rebuttal

Dr. Karen Becker stated that the sponsor's Pivotal Trial provided three evaluable cohorts. The worst case scenario analysis was required in the original IDE, but was to be replaced with actual data after completion of the Pivotal Trial. In a deficiency letter the FDA requested standard AFS scores for all trial patients.

Dr. Piantadosi pointed out the baseline differences are inconsequential. The adhesiolysis patients behave differently from all other patients, but behave similarly with their subgroup on the other continent. When the adhesiolysis variable is taken into account, the data became poolable. A subset analysis has not been employed in the sponsor's statistical review.

Dr. Rubin noted that the worst case scenario for the ITT patients was unscientific and incorrectly prejudiced the outcome results.

Dr. DeCherney explained that the AFS scores were calculated retrospectively from the modified AFS data that were gathered prospectively. Furthermore, Intergel does not incite infection in patients or in animals.

The meeting was recessed at 12:11 p.m. and was reconvened at 1:00 p.m.

PANEL DISCUSSION

Acting Panel Chair Dr. Scott Ramsey reread the questions for the panel. The first concern was **whether the statistically significant differences between Intergel and control can be considered to be clinically significant**.

Dr. D'Agostino wanted to know whether the original panel heard either the AFS derived data or the earlier modified AFS data. The sponsor stated the original panel heard the results from both data sets.

Dr. Shirk found the Pivotal Trial a test with many parameters, no control on the surgery procedures used at adhesiolysis, and 80% of the patients with no adhesions at baseline.

Dr. Gordon stated that the shift scores, which the sponsor did not have a chance to present, could address some of the issues in terms of surgical factors.

Dr. Piantadosi answered that randomization permitted reduction of bias in a large study.

Dr. Rubin added that "noisy" data (as in this study) contributed to smaller estimated effects.

Dr. D'Agostino feared that these shifting end-points were a search for a good outcome.

Dr. Piantadosi explained that consistency was tested by means of a sensitivity analysis. In this study, several assumptions or imputations were made and the outcomes were compared.

Dr. Shirk wanted to know if the protocol for the Pivotal Study was a statistically fair model and why.

Dr. Piantadosi concluded that the Pilot Study was irrelevant to understanding the results of the Pivotal Trial that was a randomized study.

Dr. Horbowyj remarked that the number of patients who had a positive result was very small.

Dr. Carlson asked if the percentage difference in adhesions was significant, since the number of adhesions in the Pivotal Study was so low.

Dr. Piantadosi replied that the protocol was a theoretical construct.

Dr. Richard Chiacchierini, Vice President, Statistics, C.L. McIntosh and Associates, stated that each patient should be taken as an independent data point with the same opportunity to generate adhesions.

Dr. Scott Ramsey noted that the problem before the panel is relative risk reduction versus absolute risk reduction.

Dr. DeCherney stated that the relative risk reduction was five-fold in the Pivotal Trial.

Dr. Gere diZerega cited that since the expected failure rate in this gynecological population is 13%, the 2% failure rate of Intergel is a great improvement.

Dr. Ramsey posed the second question, **whether the benefits of the product outweigh the risks, including any risk of infection**.

Dr. Clark asked if the infection rate in the Intergel group and the control group was clinically significant.

Dr. Mastroianni replied that the incidence of infection in this group of patients was very low.

Dr. Shirk asked what were the indications for use.

Dr. Mastroianni answered the indications included lysis of adhesions, attempted correction of infertility, and removal of ovarian cysts.

SECOND OPEN PUBLIC HEARING

Ms. Bess Weatherman, Vice Chair, National Venture Capital Association – Medical Group, warned that unexpected decisions by the regulatory agencies add risk to the association's investments. Today's decision by the FDA may influence the development of many future medical devices.

Dr. Mark Marder, Chairman of Obstetrics at Franklin Square Hospital, Baltimore, Maryland, came as a patient advocate to speak in favor of Intergel.

Dr. Melvin Thornton showed a short video documenting moderate to severe adhesions.

The meeting was recessed from 2:19 PM. until 2:31 PM.

Augusta Sisler, a patient, explained how it feels to have adhesions.

PANEL DELIBERATIONS AND VOTE

Executive Secretary Les Weinstein read the panel voting options as Approval, Approvable with Conditions and Not Approvable.

A motion was made and seconded to recommend the device for Approval. A brief discussion ensued, followed by a unanimous 4 to 0 vote in favor of approval of the device. The voting members stated the reasons for their vote for approval. After Dr. Gonzalez and Dr. Gordon made closing comments, **Acting Panel Chair Scott Ramsey** concluded that in the future he thinks this panel will be used as a last resort for dispute resolution. He also commented that the panel's vote is merely a recommendation to the CDRH Director, but he hoped that the strength of the consensus will be taken very seriously in the ultimate decision. He then thanked the panel, FDA, and the sponsors before adjourning the meeting at 2:54 p.m.

I certify that I attended the Open Session of the Medical Device Dispute Resolution Panel Meeting on September 6, 2001, and that this summary accurately reflects what transpired.

S/s

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Les Weinstein, Esq.

I approve the minutes of this meeting as recorded in this summary.

S/s

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Scott Ramsey, MD, PhD
Acting Panel Chair

Summary minutes prepared by
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